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REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University

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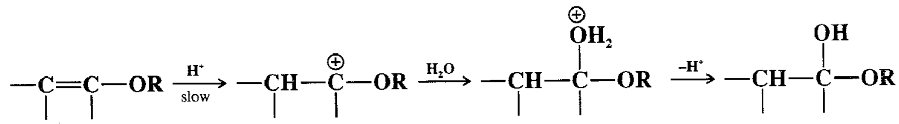
Enol ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate. However, protonation does not take place at the oxygen but at the β carbon,[495] because that gives rise to the stable carbocation **95**.[496] After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



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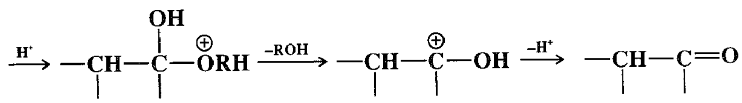
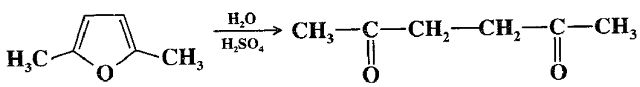


Among the facts supporting this mechanism (which is an A-SE2 mechanism because the substrate is protonated in the rate-determining step) are: (1) ^{18}O labeling shows that in $ROCH{=}CH_2$ it is the vinyl-oxygen bond and not the RO bond that cleaves;[497] (2) the reaction is subject to general acid catalysis;[498] (3) there is a solvent isotope effect when D_2O is used.[498] Enamines are also hydrolyzed by acids (see **6-2**); the mechanism is similar. Ketene dithioacetals $R_2C{=}C(SR')_2$ also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.[499] Furans represent a special case of enol ethers that are cleaved by acid to give 1,4 diones. Thus

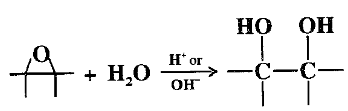


Oxonium ions are cleaved by water to give an alcohol and an ether:

$$R_3O^+\ BF_4^- + H_2O \longrightarrow R_2O + ROH + HBF_4$$

OS **I,** 67, 205; **II,** 302, 305, 323; **III,** 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV,** 302, 499, 660, 816, 903; **V,** 91, 292, 294, 703, 716, 937, 967, 1088; **VI,** 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII,** 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **68,** 25, 92; **69,** 31, 55, 148.

0-7 Hydrolysis of Epoxides
(3)*OC-seco*-hydroxy-de-alkoxy-substitution



[495]Jones; Wood *J. Chem. Soc.* **1964,** 5400; Okuyama; Fueno; Furukawa *Bull. Chem. Soc. Jpn.* **1970,** *43,* 3256; Kreevoy; Eliason *J. Phys. Chem.* **1969,** *72,* 1313; Lienhard; Wang *J. Am. Chem. Soc.* **1969,** *91,* 1146; Kresge; Chen *J. Am. Chem. Soc.* **1972,** *94,* 2818; Burt; Chiang; Kresge; Szilagyi *Can. J. Chem.* **1984,** *62,* 74.

[496]See Chwang; Kresge; Wiseman *J. Am. Chem. Soc.* **1979,** *101,* 6972.

[497]Kiprianova; Rekasheva *Dokl. Akad. Nauk SSSR* **1962,** *142,* 589.

[498]Fife *J. Am. Chem. Soc.* **1965,** *87,* 1084; Salomaa; Kankaanperä; Lajunen *Acta Chem. Scand.* **1966,** *20,* 1790; Kresge; Chiang *J. Chem. Soc. B* **1967,** 53, 58; Kresge; Yin *Can. J. Chem.* **1987,** *65,* 1753.

[499]For a review, see Okuyama *Acc. Chem. Res.* **1986,** *19,* 370-376.

The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases (see discussion of the mechanism on p. 369). Among acid catalysts the reagent of choice is perchloric acid, since side reactions are minimized with this reagent.[500] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[501]

OS **V**, 414.

B. Attack by OH at an Acyl Carbon

0-8 Hydrolysis of Acyl Halides
Hydroxy-de-halogenation

$$\mathbf{RCOCl + H_2O \longrightarrow RCOOH}$$

Acyl halides are so reactive that hydrolysis is easily carried out. In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is F < Cl < Br < I.[502] If a carboxylic acid is used as the nucleophile, an exchange may take place (see **0-74**). The mechanism[502] of hydrolysis can be either S_N1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[503] There is also evidence for the S_N2 mechanism in some cases.[504]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[505]

OS **II**, 74.

0-9 Hydrolysis of Anhydrides
Hydroxy-de-acyloxy-substitution

$$\mathbf{R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}O{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}R' + H_2O \longrightarrow R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OH + R'{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OH}$$

Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral. Only under acid catalysis does the S_N1 mechanism occur and seldom even then.[506] Anhydride hydrolysis can also be catalyzed by bases. Of course, OH^- attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 334), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[507]

[500] Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, p. 796.

[501] Berti; Macchia; Macchia *Tetrahedron Lett.* **1965,** 3421.

[502] For a review, see Talbot, Ref. 197, pp. 226-257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, in Patai *The Chemistry of Acyl Halides*; Wiley: New York, 1972, pp. 177-230.

[503] Bender; Chen *J. Am. Chem. Soc.* **1963,** *85*, 30. See also Song; Jencks *J. Am. Chem. Soc.* **1989,** *111*, 8470; Bentley; Koo; Norman *J. Org. Chem.* **1991,** *56*, 1604.

[504] Bentley; Carter; Harris, Ref. 198; Guthrie; Pike, Ref. 198. See also Lee; Sung; Uhm; Ryu *J. Chem. Soc., Perkin Trans. 2* **1989,** 1697.

[505] Bevan; Hudson *J. Chem. Soc.* **1953,** 2187; Satchell *J. Chem. Soc.* **1963,** 555.

[506] Satchell *Q. Rev., Chem. Soc.* **1963,** *17*, 160-203, pp. 172-173. For a review of the mechanism, see Talbot, Ref. 197, pp. 280-287.

[507] Butler; Gold *J. Chem. Soc.* **1961,** 4362; Fersht; Jencks *J. Am. Chem. Soc.* **1970,** *92*, 5432, 5442; Deady; Finlayson *Aust. J. Chem.* **1983,** *36*, 1951.